Remarks

Amendments

The title has been amended to reflect the scope of the claims following the response to restriction requirement.

Claim 1 has been amended to be specific to the administration of a composition containing as the sole active ingredient, milnacipran, in an amount effective to treat the chronic pain and fatigue associated with fibromyalgia. Support for this amendment is found on page 2, line 14-15, page 17, lines 1-20, and in Examples 1-3 of the specification. Claims 31-33 have been added to define specific dosage ranges. Support for new Claims 31-33 is found at page 17, lines 21-25.

The claims to combination therapy have been deleted solely to facilitate prosecution and will be pursued in a continuation application.

Rejection Under 35 U.S.C. § 103

Claims 1-9 were rejected under 35 U.S.C. § 103(a) as being unpatentable over *Medicine and Drug Journal* 37(10):238-240 (2001) to Nagaoka et al ("Nagaoka") or (WO 01/26623) to Horrobin *et al.* ("Horrobin"), in view of U.S. Patent No. 6,395,788 to Iglehart III ("Iglehart") or (WO 00/56310) to Mendel *et al* ("Mendel"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Prior Art

Nagaoka

Nagaoka reports a case history of a woman diagnosed with FMS who was treated with 30-50 mg milnacipran/day to treat depression associated with myalgia (pain of the muscle tissue, not fibrous tissue). This dosage of milnaciprin was demonstrated to reduce but not erradicate the pain associated with the myalgia, although the mental state was greatly enhanced and the authors conclude that the use of milnacipran as an antidepressant in this particular case was justified.

In any event, Nagaoka was published in October of 2001 and is therefore removed as prior art by the Declaration under 37 C.F.R. 1.131, which showed conception and reduction to practice by the applicants prior to the publication of Nagaoka.

Horrobin

Horrobin corresponds to U.S. Patent No. 6,441,038. Both the PCT application and U.S. patent are referred to jointly herein as "Horrobin". Horrobin teaches a method for treating conditions of fatigue, pain, weakness and depressed mood that are associated with neurological disorders, such as chronic fatigue syndrome, stroke, and fibromyalgia. The treatment involves administering a selective inhibitor of noradrenaline reuptake, **together with phenylalanine or tyrosine which are neurotransmitter precursors**. There is no teaching of treating these conditions solely with an inhibitor of noradrenaline uptake.

In case history number 1, the patient complained of chronic fatigue syndrome associated with FMS and tried a host of compound such as "both tricyclic and serotonin reuptake inhibiting and noradrenaline reuptake inhibiting antidepressants" which were all ineffective. It is not clear what symptoms they were trying to treat or whether a dual reuptake inhibitor, particularly an

NSRI (NE>5-HT SNRI) was used. The selective noradrenaline uptake inhibitor, Lofepramine was used with in combination with phenylalanine to treat her symptoms. They conclude that the combination of lofepramine with phenylalanine was the reason for success (page 19, lines 19-21). The patient did not respond to any antidepressant medication given without phenylalanine. This reference in fact teaches away from the claimed invention because it would inform one of skill in the art that the drug would be ineffective in the absence of phenylalanine. The compound was not administered in an *effective amount to achieve therapeutic benefit* and therefore does not satisfy the limitations in claim 1.

Case 2 describes a stroke patient who was administered a combination of lofepramine and phenylalanine to treat depression after incurring a stroke. It was concluded that this combination was effective for treating depression. It has been stated on page 12, lines 9-10 of the Applicant's specification that "treating only depression is considered ineffective for purposes of the present invention". The present method goes beyond the use of milnacipran as an antidepressant and encompasses treating symptoms of FMS such as those listed on page 1, lines 12-20. This is due in large part to the use of higher dosages, in the range of 100-250 mg milnacipran/day.

Iglehart

Iglehart discloses the use of cyclobenzaprine (a 5-HT_2 receptor antagonist), optionally together with an SNRI, to treat sleep disturbances associated with fibromyalgia. Iglehart does not disclose or suggest the use of milnacipran to treat fibromyalgia or its symptoms. Iglehart does not disclose the use of any NSRI alone to treat fibromyalgia or its symptoms. Iglehart does

not provide any motivation to teaching to modify the references of Nagaoka or Horrobin to derive the claimed invention.

Mendel

Mendel teaches the use of N, N,-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine-HCl (sibutramine), and closely related cyclobutyl compounds for treating CFS. Mendel teaches that sibutramine inhibits reuptake of all three monoamines (5-HT, NA, and DA). Mendel does not teach a serotonin-noradrenaline reuptake inhibitor. Further, milnacipran is an unrelated *cyclopropyl* based compound. Mendel does not teach a single compound with the chemical structure of Milnacipran for treating FMS.

The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary

references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

The Court of Appeals for the Federal Circuit recently warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the teaching or motivation to combine prior art references." In re Dembiczak, 175 F.3d 994 at 999 (Fed. Cir. 1999). While the suggestion to combine may be found in explicit or implicit teachings within the references, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved, the "question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. WMS Gaming, Inc. v International Game Technology, 184 F.3d 1339 at 1355 (Fed. Cir. 1999) . "The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular." In re Dembiczak, 175 F.3d 994 at 999 (Fed. Cir. 1999). The references must themselves lead those in the art to what is claimed. And in this case, there is simply no such teaching.

It has been made very clear that "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir.

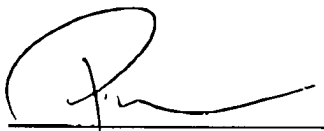
1991). Further, the "level of skill in the art cannot be relied upon to provide the suggestion to combine references. Al-site Corp v. VSI Int'l Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). In the present case, there is no teaching in the prior art that would suggest combining the references, and the Applicants have also achieved unexpected results.

Nagaoka or Horrobin in combination with Mendel or Iglehart

Nagaoka does not teach the doses used in the present method. Horrobin does not teach using milnaciprin alone. Mendel and Iglehart do not address these deficiencies nor do they provide the motivation to combine these references and then modify the result as applicants have done, with a reasonable expectation of success in treating pain and fatigue associated with fibromyalgia. One of skill in the art would not be motivated to combine these references and derive the present method for treating the chronic pain and fatigue associated with FMS by administering milnaciprin.

Allowance of claims 1-9 and 31-33 is respectfully solicited.

Respectfully submitted,



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Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, **INSERT DATE OF FILING**, to the Commissioner for Patents, U.S. Patent and Trademark Office, Washington, DC 20231.

Jean Hicks

Date: February 11, 2003

Marked Up Version of Amended Claims
Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (Twice Amended) A method of treating fibromyalgia syndrome (FMS)[, physiological symptoms associated therewith in an animal subject, or a combination thereof, the method] comprising administering to an animal subject suffering from FMS, [an effective amount of] a composition comprising as the active ingredient milnacipran, or a pharmaceutically acceptable salt thereof in an amount effective to treat the chronic pain and fatigue associated with FMS.

Please cancel claims 2-6.

7. The method according to claim 1, wherein the animal subject is human.

8. (amended) The method according to claim 1, wherein the amount of milnacipran administered is from about 25 mg to about 400 mg per day.

9. The method according to claim 1, wherein the milnacipran is formulated in a sustained release formulation.

31. The method of claim 1 wherein the amount of milnacipran administered is at least 100 mg per day.

32. The method of claim 1 wherein the amount of milnacipran administered is between 100 and 400 mg per day.

33. The method of claim 1 wherein the amount of milnacipran administered is between 100 and 250 mg per day.